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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/646,308	08/21/2003	Paul B. J. Burton	3432-US-NP	9578

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EXAMINER	
JIANG, DONG	
ART UNIT	PAPER NUMBER
1646	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/646,308	BURTON ET AL.	
	Examiner	Art Unit	
	DONG JIANG	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 March 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *31-53 and 55-67* is/are pending in the application.

4a) Of the above claim(s) *31-45,53 and 55-62* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *46-52 and 63-67* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *31-53 and 55-67* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED OFFICE ACTION

The request filed on 18 March 2009 for a Continued Examination (RCE) under 37 CFR 1.114 based on parent Application No. 10/646,308 is acceptable, and a RCE has been established. An action on the RCE follows.

Applicant's amendment filed on 18 March 2009 is acknowledged and entered. Following the amendment, claims 46 and 67 are amended.

Currently, claims 31-53 and 55-67 are pending, and claims 46-52 and 63-67 are under consideration. Claims 31-45, 53 and 55-62 remain withdrawn from further consideration as being drawn to a non-elected invention.

Withdrawal of Objections and Rejections:

The rejection of claim 67 under 35 U.S.C. 112, second paragraph, as being indefinite is withdrawn in view of applicant's amendment.

Rejections under 35 U.S.C. §112:

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 46-52 and 63-67 remain rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for claims limited in scope to a method for reducing chronic cardiotoxicity caused by a chemotherapeutic agent with a 4-1BB antagonist, does not reasonably provide enablement for claims to a method for *preventing* chronic cardiotoxicity caused by a chemotherapeutic agent with a 4-1BB antagonist. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use

the invention commensurate in scope with these claims, for the reasons of record set forth in the last Office Action mailed on 18 September 2001, at pages 2-3.

Applicants argument filed on 18 March 2009 has been fully considered, but is not deemed persuasive for the reasons below.

At pages 6-7 of the response, applicants point out the support in the specification (Example 7, for example) as that blocking 4-1BB-L/4-1BB signaling prevented Adriamycin-induced cardiomyopathy; "...no mortality was observed in the 4-BB-L KO mice and none of the 4-1BB-L KO mice showed signs of the most severe cardiotoxacity following Adriamycin challenge compared to 50 to 70% of the wild type mice"; and "[T]hese data [presented in Example 7] establish a sound basis for preventing, treating, or alleviating the symptoms of cardiovascular disease...". Applicants further argue that it is clear from the application that antagonists capable of completely blocking 4-1BB and 4-1BB-L signaling would prevent Adriamycin-induced cardiomyopathay; and the application describes and enables *preventing as* well as reducing chronic cardiotoxieity. This argument is not persuasive for the following reasons: first, "preventing" would necessarily mean that a subject would be given a 4-1BB antagonist, and such administration would forbid said cardiotoxicity from happening. However, that is not the case here because no mortality or lack of signs of *the most severe* cardiotoxacity is not equal to lack of cardiotoxicity. As shown in Example 7 (Table 3), 43% of the 4-BB-L KO mice showed progressive cardiac dysfunction (class III), and 50% showed total cardiotoxicity (vs. 71% of the wild type mice). All that the results indicate is that administration of 4-1BB antagonist could *reduce* said cardiotoxicity, and it *did not prevent* the cardiotoxicity from happening.

Claims 46-49 and 52 remain rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention, for the reasons of record set forth in the previous Office Actions mailed on 11/15/07 and 9/18/08.

Applicants argument filed on 18 March 2009 has been fully considered, but is not deemed persuasive for the reasons below.

At page 7 of the response, applicants argue that the examiner has appeared to take the position that the application must contain a written description of every possible antagonistic of 4-1BB/4-1BB-L, its "complete or partial structure, physical and/or chemical properties, functional characteristics, methods of making" etc.; and that it is not required that every possible embodiment of antagonist needs to be described to fulfill the requirements of 35 U.S.C. §112, first paragraph. Applicants further argue that claim 46 recites a *method* of preventing or reducing chronic cardiotoxicity comprising administering a 4-1BB antagonist, and the basis for this method is clearly found in the specification; that clearly, the inventors had possession of the claimed method by identifying and demonstrating the connection between antagonizing 4-1BB-L:4-1BB signaling and preventing or reducing Adriamycin-induced cardiotoxicity, as shown in the data of Example 7, which is the basis for the claimed method of claim 46, not a recitation of every possible antagonist of 4-1BB. This argument is not persuasive because the issue is not whether the method of reducing said cardiotoxicity using a 4-1BB antagonist is *enabled* (i.e., the connection between antagonizing 4-1BB-L:4-1BB signaling and reducing said cardiotoxicity provided the basis for enablement of the method), rather, the issue is that the instant disclosure does not provide adequate written description for the claimed genus of 4-1BB antagonist. The written description requirement is separate and distinct from the enablement requirement (MPEP 2161). Further, the examiner never takes the position that the application must contain a written description of every possible antagonistic of 4-1BB/4-1BB-L, it is the instant application, which merely provides limited numbers of species of 4-1BB antagonists. Such limited numbers of species are not sufficient to represent unlimited number of structurally dissimilar functional equivalents of 4-1BB antagonists encompassed by the claimed genus (see last Office Action). "A description of what a material does, rather than of what it is, usually does not suffice." *Rochester,* 358 F.3d at 923; *Eli Lilly,* 119 at 1568. Instead, the "disclosure must allow one skilled in the art to visualize or recognize the identity of the subject matter purportedly described." *Id.*

Rejections Over Prior Art:

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 C.F.R. 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Claims 46-52 are rejected under 35 U.S.C. 103(a) as being unpatentable over Waelti (US2004/0028687) and Yudestad et al. (Cardiovasc Res., 2002 Apr; 54(1):175-82, provided by applicants), and in view of Goodwin et al. (US5,674,704, provided by applicants), for the reasons of record set forth in the previous Office Actions mailed on 11/15/07 and 9/18/08, and for the reasons below.

The teachings of Waelti, Yudestad and Goodwin were reviewed in the previous Office Action (11/15/07), and are paraphrased herein:

Waelti teaches that one of the greatest limitations of cancer chemotherapy are the severe side effects accompanying the use of some of the most broadly active antitumor agents, for example, anthracycline compounds, such as doxorubicin, have a very wide spectrum of anticancer activity, but their side effects include, among others, dose-dependent cardiotoxicity often resulting in irreversible cardiomyopathy with serious congestive heart failure ([0022], bridging pages 2 and 3).

Yudestad discloses that there is increased gene expression of several TNF superfamily ligands in PBMC of patients with chronic heart failure, including, among others, 4-1BB-L; that in particular, the enhanced expression of ligands in the TNF superfamily may reflect a potential

pathogenic role of these cytokines in the progression of CHF (abstract); that enhanced expression of several ligands in the TNF superfamily in PBMC infiltrating the failing myocardium may contribute to the development of myocardial failure, which may in turn lead to further activation of leukocytes within the myocardial circulation, representing a vicious circle in the pathogenesis of CHF (page 181, lines 15-22). Additionally, Yudestad teaches that inflammatory cytokines have been shown to induce pathological events in CSF, for example, overexpression of TNFα or infusion of TNFα has been shown to cause a dilated cardiomyopathy-like phenotype mimicking several aspects of clinical heart failure, indicating that both circulating and locally produced cytokines may induce myocardial dysfunction (page 175, the paragraph bridging the two columns). Further, Yudestad teaches that whereas there is strong evidence for TNFα as a pathogenic factor in CHF, other members of the TNF superfamily may potentially be even more important (page 176, lines 6-9 of the 1st column).

Goodwin teaches soluble 4-1BB polypeptides, which retain the ability to bind the 4-1BB ligand (column 4, lines 23-28); and fusion proteins thereof comprising a soluble 4-1BB and the constant region of an antibody (the paragraph bridging columns 5 and 6). Further, Goodwin teaches soluble forms of 4-1BB proteins are advantageous for certain applications, such as being administered intravenously for therapeutic purposes (column 4, lines 53-56).

It would have been obvious to the person of ordinary skill in the art at the time the invention was made to use Goodwin's soluble 4-1BB fusion for the treatment of cardiomyopathy/CHF including those caused by anthracycline compounds such as doxorubicin (taught by Waelti), as Yudestad teaches that 4-1BB-L, a member of the TNF superfamily, is overexpressed in CHF patients; while TNFα is a pathogenic factor in CHF, other members of the TNF superfamily may potentially be even more important; and that the enhanced expression of ligands in the TNF superfamily may reflect a potential pathogenic role of these cytokines in CHF. The person of ordinary skill in the art would have been motivated to do so for treating cardiomyopathy/CHF, and reasonably would have expected success because Goodwin has teaches that the soluble 4-1BB retains the ability to bind the 4-1BB ligand, therefore, it would prohibit the binding of the 4-1BB ligand to its receptor, and is a 4-1BB antagonist.

Applicants argument filed on 18 March 2009 has been fully considered, but is not deemed persuasive for the reasons below.

At page 8 of the response, applicants argue that none of the patients screened in Yndestad was suffering from chronic cardiotoxiciry caused by a chemotherapeutic agent, specifically, an anthracycline drug, such as doxorubicin; that the instant claimed method is drawn to a method of preventing or reducing chronic cardiotoxicity caused by a chemotherapeutic agent, and yet the Examiner has cited as the primary reference a study of CHF patients; that the examiner has not provided may reference which provides evidence that one of ordinary skill in the art could assume or find it obvious that the increased gene expression found with CHF patients described in Ynedstad would be the same for patients suffering from the chronic cardiotoxicity caused by doxorubicin, indeed, the Examiner herself has characterized these two conditions as different, distinct medical conditions (restriction). This argument is not persuasive because, as addressed above, Waelti (the primary reference now) teaches that anthracycline compounds, such as doxorubicin, have a very wide spectrum of anticancer activity, but their side effects include, among others, dose-dependent cardiotoxicity often resulting in irreversible cardiomyopathy with serious congestive heart failure; and Yudestad teaches that 4-1BB-L, a member of the TNF superfamily, is overexpressed in CHF patients; while TNFα is a pathogenic factor in CHF, other members of the TNF superfamily may potentially be even more important; and that the enhanced expression of ligands in the TNF superfamily may reflect a potential pathogenic role of these cytokines in CHF. As such, it would be obvious to target other members of the TNF superfamily, such as 4-1BB-L, which are overexpressed in CHF patients including those caused by the treatment of anthracycline compounds.

At pages 8-9 of the response, applicants argue that the Examiner is relying on hindsight based on the disclosure in the instant application for the basis of her 3S U.S.C. § 103 (a) rejection, which is not permissible in making a 103 rejection; and that it was only the data contained in the instant application, such as the results from in Examples 7 and 8, that demonstrated that antagonizing 4-1BB would prevent or reduce chronic cardiotoxicity caused by a chemotherapeutic agent, and there is no reference provided by the Examiner that showed upregulation of 4-1BB for such a patient population. This argument is not persuasive for the reasons addressed above. Further, it must be recognized that any judgment on obviousness is

in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

Conclusion:

No claim is allowed.

Advisory Information:

Any inquiry concerning this communication should be directed to Dong Jiang whose telephone number is 571-272-0872. The examiner can normally be reached on Monday - Friday from 9:30 AM to 7:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Nickol, can be reached on 571-272-0835. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Dong Jiang/
Primary Examiner, Art Unit 1646
5/8/09